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Detection of epileptic spikes by magnetoencephalography and electroencephalography after sleep deprivation

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ABSTRACT

Introduction: In diagnosis of epilepsies electrophysiological findings play a key role. While spontaneous electroencephalography (EEG) and EEG with sleep deprivation (EEGsd) are widely evaluated and used, application of magnetoencephalography (MEG) in this field is primarily limited to presurgical assessment of focal epilepsies.

Methods: In this study we retrospectively compared MEG (M/EEG) and EEGsd in 63 (55) patients with focal and generalized epilepsy with regard to occurrence of epileptic spikes.

Results: MEG could record epileptic spikes in 38 patients (60%), while EEGsd recorded spikes in only 32 patients (51%). In a group of 55 patients simultaneous MEG/EEG (M/EEG) was able to record spikes in 38 patients (71%) compared to epileptic spikes in 28 patients (51%) recorded by EEGsd. In a subgroup of 17 MR-negative patients simultaneous M/EEG could record epileptic spikes in all patients, while EEGsd was successful in only 11 (64%) of them.

Conclusion: In this study, MEG showed a tendency to record epileptic spikes in more patients than EEGsd. Furthermore, simultaneous M/EEG has been shown to be especially successful in detection of epileptic spikes in patients with MR-negative epilepsy. This might at least in parts be explained by neocortical predominance of MR-negative epilepsy. Thus, this study motivates prospective studies to evaluate the substitutability of EEGsd by MEG more extensively.

1. Introduction

Electrophysiological findings are essential for diagnosis and treatment of focal and generalized epilepsies.[1] Since surface EEG recordings are negative for epileptic discharges in about 50–80% of all epilepsy patients having their first EEG,[2] sleep deprivation is used to increase sensitivity of EEG for epileptic activity.[3] One review describes an increase in recorded interictal epileptic discharges (IED) in EEGsd of 30–70% and suggests an activation of epileptic activity of 10–30%.[4] However, significance of EEGsd in diagnosis of epilepsy is still debated. Some authors even find insufficient evidence for the increase of diagnostic information of EEGsd.[5,6] Moreover EEGsd is a patient unfriendly diagnostic tool, as it stresses them with changes in diurnal sleep–wake rhythm and it possibly causes seizures.[7–9]

In contrast, current major clinical use of magnetoencephalography (MEG) is presurgical evaluation of epilepsy patients for focus localization and functional mapping.[10–13] As MEG and EEG are complementary in their nature, combination of both was found to be useful.[14] Despite this widely established role of presurgical MEG, there is a lack of systematic research at present, which evaluates value of simultaneous M/EEG in early evaluation of epilepsy patients compared to standard EEG procedures. Just one recent study with 51 patients reports a diagnostic yield of MEG after inconclusive first EEG in patients with suspicion of neocortical focal epilepsy.[15] In this study, diagnostic gain of MEG in diagnosis of epilepsy after inconclusive spontaneous EEG was comparable to EEG in sleep-deprived patients.

In the comparison of M/EEG and EEGsd for epileptic spike yield, clinical value of these findings would be even higher in patient with normal magnetic resonance imaging (MRI) studies. Localizations of epileptic spikes recorded by MEG could, e.g., be used to guide magnetic resonance spectroscopy and fiber tracking to detect cortical and subcortical changes in subtle cortical lesions.[16,17]

In the presented work, we retrospectively compare MEG and M/EEG to EEGsd with regard to their ability to detect epileptic spikes in patients with diagnosis of focal or generalized epilepsy. In subgroup analyses, relations of electrophysiological findings from the different modalities are compared to results from structural MRI studies and to the site of the suspected epileptogenic focus.

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2. Materials and methods

2.1. Study outline

In this study, patients with focal and generalized epilepsy, who had EEGsd and MEG recordings, were included. Recordings were compared by the occurrence of epileptic spikes. If at least one epileptic spike was detected, this recording was counted as positive. Parts of the study population had simultaneous M/EEG instead of MEG. In these cases M/EEG was compared to EEGsd, too. In further subgroup analyses, the occurrence of epileptic spikes in MEG (M/EEG) and EEGsd was compared in patients with negative/positive structural MRI and in patients with neocortical/temporomesial focus hypotheses (Fig. 1).

2.2. Sleep deprivation EEG (EEGsd)

Typical indications for EEGsd were (a) an unremarkable EEG without sleep deprivation in patients with clinical suspicion of epilepsy, (b) reappraisal of diagnosis after referral from ambulant care/other hospitals and (c) admission for presurgical epilepsy monitoring in patients with focal epilepsy. For EEGsd examination, partial sleep deprivation (PSD) was used. 24 h before EEGsd, patients were allowed to sleep between 2 and 6 am. 10 min before each EEGsd, 0.5 mg/kg doxylaminsuccinat was administered orally to every patient to increase fatigue and to facilitate sleep. Although literature is rare on the use of this drug during EEG recordings, it is not known to influence spike yield by itself. Each EEGsd had a length of 30–40 min. Recordings began with hyperventilation for 3 min followed by 2 min rest. Afterwards, patients were asked to sleep, because sleep is known to increase occurrence of interictal epileptic discharges.[2] Time span for sleep was 20 min and prolonged for 5–10 min, if patient had problems falling asleep. After sleep, intermittent photic stimulation (IPS) was performed according to the European standard,[18] as sleep deprivation increases chance of photoparoxysmal response.[19] Each stimulus lasted for 10 s (eyes opened and closed) with 7 s inter-stimulus interval. IPS was followed by 2 min of rest at the end of recording.

EEGsd was recorded according to the 10/20 system with additional ear electrodes. Recordings were digitized with a sampling rate of 256 Hz, a resolution of 16 bit and stored digitally using a digital EEG system (Natus Europe GmbH, Division IT-med, Usingen, Germany).

If multiple EEGsd were recorded in one patient, EEGsd closest in time to MEG recording, was chosen. For this study, clinical reports of EEGsd findings were used, therefore, results are not biased by a possible intention of the authors of the manuscript. Experienced neurologists evaluated EEGsd with regard to occurrence of epileptic spikes (sharp epileptiform transient with a pointed peak, which differs from background activity[20]). If clear epileptic spikes were recognized in EEGsd, the recording was considered positive.

2.3. M/EEG procedure

MEG was performed using a 74 channel MEG system (4D Neuroimaging, San Diego, CA, USA) in a magnetically shielded room (Vakuumschmelze, Hanau, Germany). It consists of two sensors (sensors A and B) with 37 first-order gradiometers with a 5 cm baseline. Distance between the channels was 2.8 cm on average. A 32-channel EEG system was used for simultaneous EEG recordings. MEG recordings were typically performed during evaluation of patients with drug resistant focal or generalized epilepsy. In single cases, MEG was performed in earlier diagnostic evaluation of epilepsy.

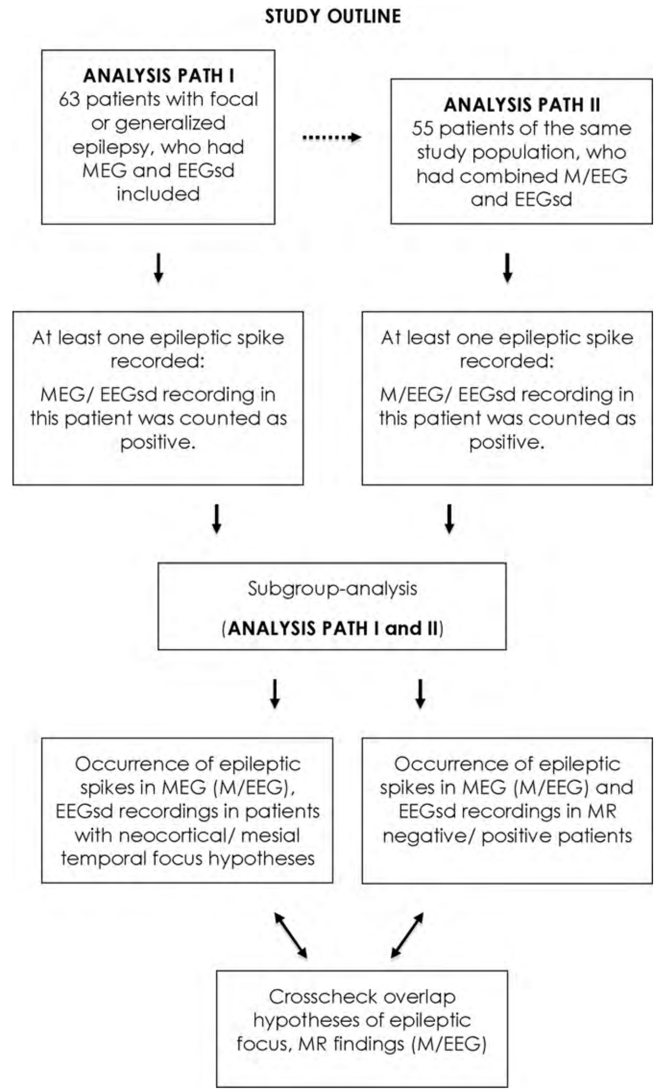

Fig. 1. Study outline.

For M/EEG recordings patients were positioned in supine position with eyes closed. No provocation methods for interictal epileptic activity were used.

During recording-sessions of each patient, MEG-sensors were repositioned to different recording positions allowing investigation of multiple brain regions. Recording length was 20 min for each sensor position (‘run’). For this study, runs with sensor A primarily positioned over brain areas with hypotheses for epileptic foci from video-EEG monitoring and MRI was chosen for comparison to EEGsd. Furthermore in subsequent runs sensor A was moved to different brain areas, so that recordings were taken from multiple areas over both hemispheres. In patients with suspicion of idiopathic generalized epilepsy, sensor A was positioned bifrontally and subsequently to other bilateral recording sites. Data from sensor B were omitted. In all MEG recordings included in this study, recording duration for each sensor position was 20 min. So it was ensured that MEG recording duration was always shorter than that of EEGsd.

MEG signal was processed by an analog bandpass filter (1–120 Hz) and digitized with a sampling rate of 520.8 Hz. Afterwards, M/EEG recordings were digitally bandpass-filtered (3–70 Hz, notch filter 50 Hz). These settings were based on in-house standard for clinical routine investigations.

If multiple MEG or M/EEG were recorded, MEG or M/EEG was chosen, which was closest in time to EEGsd recording. If MEG was recorded after EEGsd, patients were only included in this study, if there was a time span of at least 1 week after EEGsd. So an effect of sleep deprivation on spike detection in MEG has been avoided, but changes in clinical status or medication may have occurred. MEG recordings were manually assessed for epileptic spikes by experienced examiners. Epileptic MEG spikes were chosen according to the characteristics used for EEG.[20,21] For this study, clinical reports of MEG findings were used to avoid interpretational bias.

2.4. MRI procedure

All patients included in this study had an in-house high-resolution epilepsy MRI as structural imaging of the brain. In-house MR imaging was performed at 3 T Magnetom Trio or 1.5 T Magnetom Sonata (both Siemens Medical Solutions, Erlangen Germany) with 8-, respectively 32-Channel Head Array coil including the following sequences: (1) 3D-fluid-attenuated-inversion-recovery (3D-FLAIR) sequence (1 mm slices), (2) coronal T2w (3 mm slices) and coronal inversion recovery (IR, 3 mm slices) sequences perpendicular to the long axis of the hippocampi, (3) T2*w gradient echo sequence (FLASH), (4) T1-3D-MPRAGE (1 -mm^2-voxel), (5) axial T1w Gadolinium enhanced sequence (4 mm slices). MRI-scans were rated as MR-negative, if experienced neuroradiologists could not detect at least one possibly epileptogenic lesions. Otherwise they were rated as MR-positive.

2.5. Statistics

Statistical analysis was performed using SPSS 17 for windows (SPSS Inc., Chicago, IL, USA). For group comparisons, two-tailed chi-square test was used to reject the null-hypotheses: (i) that the appearance of epileptic spikes in MEG (M/EEG) and EEGsd recordings is equal, (ii) that the appearance of epileptic spikes in M/EEG recordings in patients with MR-negative/MR-positive epilepsy is equal.

2.6. Subjects

Patients (mean age: 34 years, range: 14–59 years) with diagnosis of focal or generalized epilepsy who had an EEGsd and M/EEG at the Epilepsy Center Erlangen between years 2000 and 2008 were included in this retrospective study. 63 patients participated in this study. 60 had focal epilepsies and 3 were diagnosed having idiopathic generalized epilepsies. 43 patients had symptomatic epilepsies of different causes (Fig. 2). 54 of all 63 patients had a clinical hypothesis of the epileptic focus based on findings from video-EEG monitoring, structural MRI, MEG, neuropsychological assessment and in selected cases SPECT, PET, or they were diagnosed as having idiopathic generalized epilepsy. 37 of them had hypothesis of neocortical epileptic focus, while in 17 patients epileptic focus hypothesis was temporomesial. All patients were on average treated with two antiepileptic drugs (AED) (range 0–3). Medication changes between MEG and EEGsd averages on change of one drug. Details about patients are listed in Table 1. We examined a heterogeneous group of patients in this study, since we had to analyze a group of patients treated of our epilepsy center. As MEG at our epilepsy center is most often recorded during presurgical evaluation in patients with drug

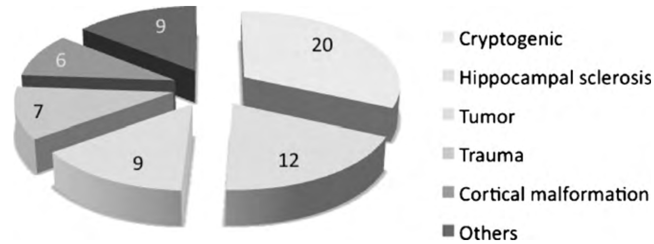

Fig. 2. Etiologies of epilepsies of all patients with focal and generalized epilepsies included in this study.

resistant focal epilepsies, most of the patients included in this study were in advanced treatment steps of their disease.

In five patients, two EEGsd were recorded. 15 patients had two MEG sessions and two other patients had three sessions, mean time span between EEGsd and run of MEG chosen for this study was 7 months. In 55 patients, an EEG simultaneous to MEG was recorded in the run used for assessment in this project. 42 epilepsies were MR-positive and 21 were MR-negative.

3. Results

3.1. EEGsd M/EEG and MRI

In 63 patients (60 patients with focal and 3 patients with idiopathic generalized epilepsy) spikes were recorded in 60% by MEG, while EEGsd could record spikes in 51%. Statistical comparison using two-tailed chi-square test showed, that there was a strong tendency of MEG to record epileptic spikes in more patients than EEGsd ($p = 0.057$). MEG was positive in 15 patients, for whom EEGsd was negative. In contrast, EEGsd was positive in only 9 patients, in whom MEG was negative (Fig. 3A).

In 55 patients, from the same study population, in whom simultaneous M/EEG was performed, spikes were recorded by at least one of both simultaneous modalities in 71% (positive in 39 patients). The percentage of patients in whom EEGsd could record epileptic spikes in this group of patients remained 51% (positive in 28 patients). No statistically significant difference between M/EEG and EEGsd could be found. But detection of epileptic spikes in patients without epileptic spikes in EEGsd was possible in 17 patients by simultaneous M/EEG (Fig. 3B).

Analysis of MR-negative patients versus MR-positive patients, who had simultaneous M/EEG showed a highly significant difference of spikes recorded by combined M/EEG for MR-negative patients compared to patients who were MR-positive using two-tailed chi-square test ($p < 0.001$). EEGsd recordings could not show a significant difference between these groups (Fig. 3C and D).

In the group of 21 MR-negative patients, 15 patients had epileptic spikes in MEG and 13 had spikes in EEGsd. In patients with simultaneous M/EEG, the effect was more pronounced: in all 17 patients with MR-negative epilepsy, epileptic spikes could be recorded by M/EEG. In contrast, EEGsd was able to record epileptic spikes in only 11 of these patients.

Furthermore MEG (M/EEG) and EEGsd appeared to be equally effective in recording epileptic spikes in patients with neocortical and mesial temporal lobe epilepsy in the group of 54 patients with

Table 1
Patient characteristics; AED: antiepileptic drugs, FE: focal epilepsy, IGE: idiopathic generalized epilepsy.

	Age (years)	Epilepsy duration (years)	Number AED	FE/IGE (number of patients)	Hypotheses of epileptic focus	MR-positive/ MR-negative
Female 37/male 26	Mean: 34 (range 14–59)	Mean: 18 (range 1–55)	Mean: 1.9 (range 0–3)	60/3	9 no hypotheses 37 neocortical 17 temporomesial	42 MR-positive, 21 MR-negative

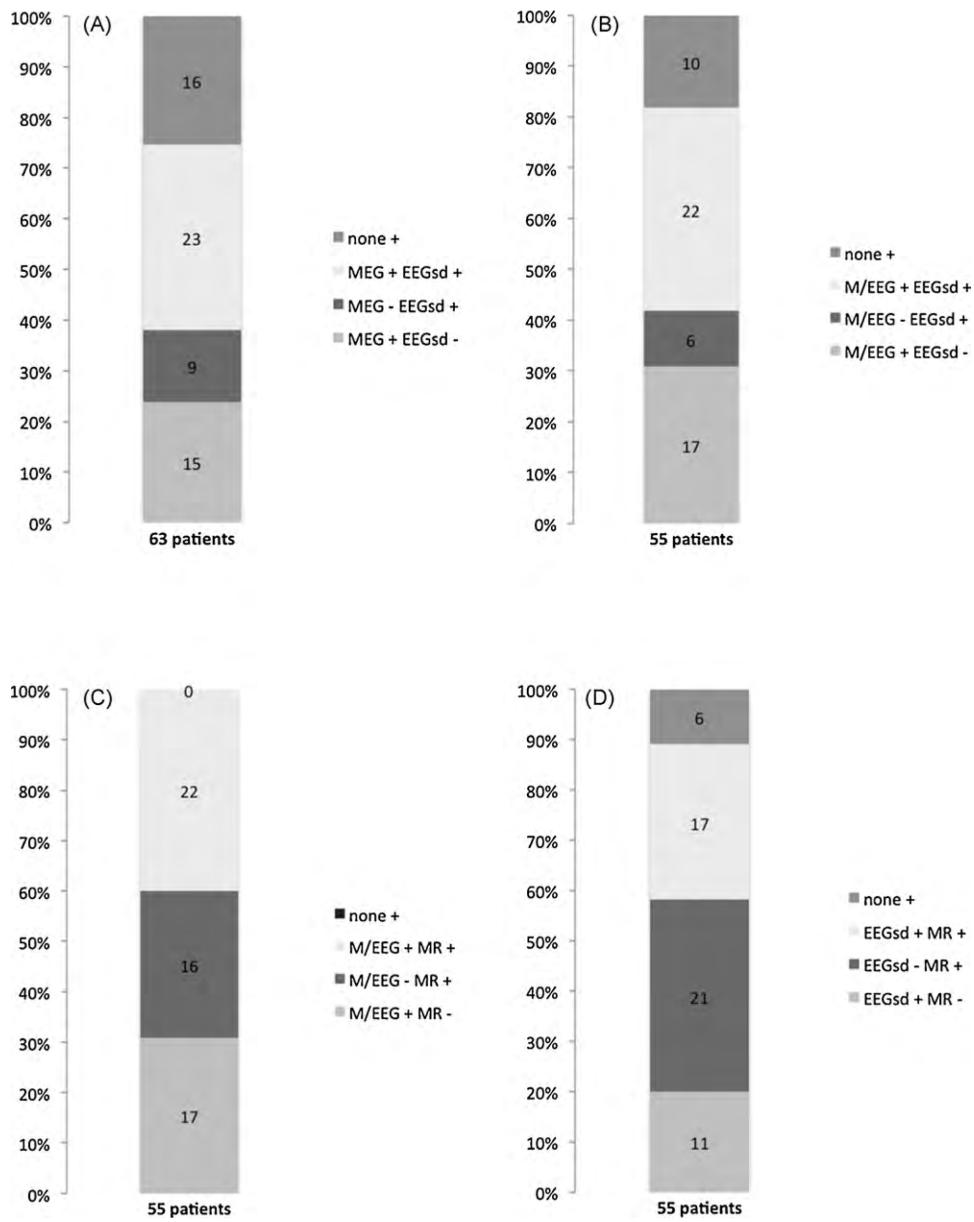

Fig. 3. (A) Sensitivity of MEG compared to EEGsd in all patients of this study; (B) sensitivity of M/EEG compared to EEGsd in all patients who had simultaneous M/EEG and EEGsd; (C) comparison of sensitivity of M/EEG and MR-positive/negative patients in all patients who had simultaneous M/EEG and (D) comparison of EEGsd and MRI in the same group of patients. *y*-Axis: percent, *x*-axis: total number of patients included in this analysis, labels: total number of patients in each group.

clinical focus hypotheses. Nevertheless in patients with mesial temporal lobe focus, MEG and simultaneous M/EEG had the tendency to record epileptic spikes more frequently than EEGsd. A detailed illustration of the comparison between M/EEG, EEGsd, MR findings and hypotheses for the epileptic focus is given in Fig. 4.

In general, dipoles localized from epileptic spikes recorded by MEG could be used for planning of epilepsy surgery, which was performed in 12 patients. However, the role of MEG in presurgical planning, relation of dipole localizations to resection volume and post surgery outcome was not analyzed for this study, as this information was only available in MEG (M/EEG) and not for EEGsd. It is discussed elsewhere in full detail.[12,13,22]

4. Discussion

In this study, epileptic spikes tend to occur more often in MEG recordings compared to EEGsd in a group of patients with diagnosis of focal and generalized epilepsies. Prior studies already demonstrated that MEG has a tendency to be more sensitive for epileptic activity than surface EEG without sleep deprivation, especially in patients with neocortical epilepsy.[24–26] In additional prior MEG-studies, it could be shown, that sensitivity of MEG for epileptic activity is about 70%.[13,27] Sensitivity of EEGsd for epileptic spikes remains unclear as protocols vary, but may be estimated between 30 and 70%. Another study with 51 patients found equal yield of clinical information of EEGsd and MEG in patients with suspicion of epilepsy.[15] In addition to the results of this study, the study on hand investigated the use of simultaneous M/EEG and a subgroup analysis for MR-negative patients and MR-positive patients, respectively was done: the supplementary nature of MEG and EEGsd could be demonstrated in the presented study, as it has been described before.[14] Although fraction of patients with recorded epileptic spikes using simultaneous M/EEG increased to 71%, no statistically significant difference could be

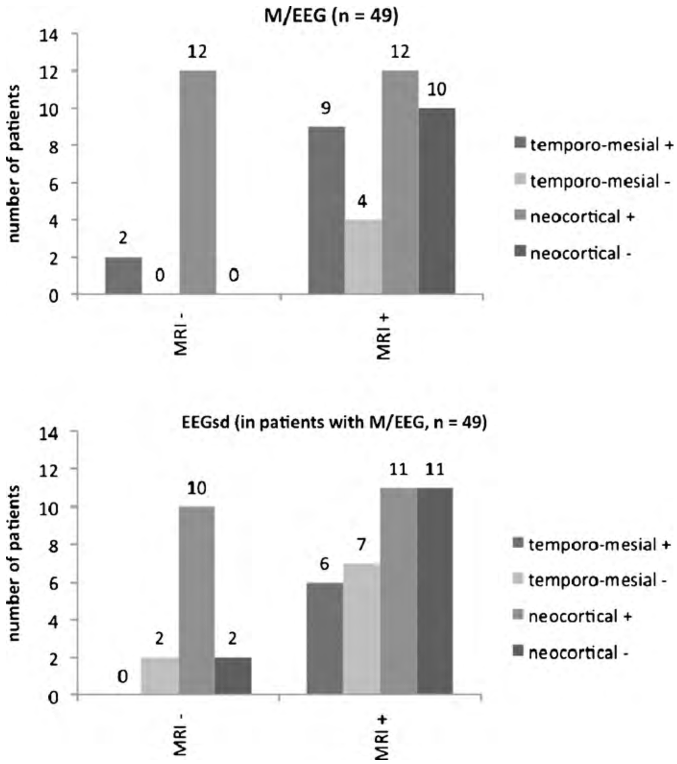

Fig. 4. This figure shows the relation of M/EEG and EEGsd recordings to MRI findings and focus hypotheses. Positive/negative M/EEG (upper part) and EEGsd (lower part) in patients who had simultaneous M/EEG with MR-negative/-positive epilepsy and neocortical/temporomesial hypotheses of the epileptic focus ($n = 49$ patients). In contrast to EEGsd M/EEG recorded epileptic spikes in all MR negative patients, while negative MRI was more often related to neocortical focus hypothesis. In MR positive cases M/EEG also recorded more often epileptic spikes than EEGsd. This effect was even more pronounced in patients with temporo-mesial focus hypothesis.

shown between simultaneous M/EEG and EEGsd. A decreased cohort size of respective patient groups possibly caused this. Combination of M/EEG also creates a larger overlap of patients with recorded spikes in M/EEG and EEGsd, since simultaneous EEG records the same modality as EEGsd. However, simultaneous M/EEG has shown to be as effective to register epileptic spikes as EEGsd. In contrast, in all MR-negative patients, who had simultaneous M/EEG (epilepsy etiology: 16 cryptogenic, 1 posttraumatic), epileptic spikes could be recorded with M/EEG. With EEGsd, in only 64% of these cases, epileptic spikes were recorded. An explanation may be, that MEG is especially sensitive for epilepsies caused by subtle neocortical lesions,[24,28,29] which might be more often MR-negative than typical mesial temporal lesions. The small overlap of temporomesial hypotheses of the epileptic focus and negative MRI (2 patients; Table 2) is in support of this hypothesis. The limiting factor in this comparison is that in only 49 patients there is an existing hypothesis of the epileptic focus with coexisting M/EEG findings.

From a clinical point of view findings from MEG source localization are highly valuable and could guide identification of subtle structural cortical or subcortical lesions, e.g., by diffusion tensor imaging (DTI) and single voxel proton magnetic resonance spectroscopy.[16,17,30]

In contrast to the popular appraisal,[32] that MEG is less sensitive for mesial temporal lobe epilepsy than EEG, in our study MEG (M/EEG) could record epileptic spikes in as many patients as EEGsd (Table 2).

As electrophysiological findings are of great clinical importance in diagnosis[31] and treatment monitoring,[32] a diagnostic tool like MEG and M/EEG, which registers epileptic spikes by trend more often than EEGsd would be very useful. Furthermore, localization information from MEG may be used to identify the epileptogenic zone in focal epilepsies[33–35] and to characterize the epileptic network in patients with IGE.[23] 12 patients of this study with recorded spikes in MEG underwent epilepsy surgery. In general, MEG focus localization could be used for planning of the surgical intervention, although role of MEG in surgical planning was not object of this work. Characterization of involved epileptic networks in patients with IGE may be used to optimize antiepileptic treatment.

Comparability of MEG (M/EEG) recordings and EEGsd in this study may be seen as limited, as there are some differences between them. Because it was the goal of this project to compare the appearance of epileptic spikes retrospectively in two clinical diagnostic methods, it was clear that certain aspects had to remain distinct. The most important of them are discussed in the following: MEG and M/EEG had a higher sensor density. But the higher number of MEG channels compared to EEG electrodes did not improve sensitivity of MEG trials in a recent study.[15] However, high sensor density may be very useful in localization of epileptic activity.[36] In contrast, sensitivity of MEG and M/EEG for epileptic spikes could have been diminished by recording length, which was 10–20 min shorter than that of EEGsd. Furthermore, for MEG no provocation methods like hyperventilation, sleep or IPS were used unlike for EEGsd, although these procedures are known to increase sensitivity for epileptic activity.[2,18] The use of doxylaminsuccinat for EEGsd in this study might be disputed, as it was not used for MEG recordings. During EEGsd it facilitated to fall asleep. Although the literature is rare, there is no hint, that it might influence the appearance of epileptic spikes more than that it helps falling asleep.

Also caused by the retrospective nature of this study, further limitations have to be mentioned: mean distance in time between MEG (M/EEG) and EEGsd recordings was several months. In this time span, AED changed on average by one drug and changes in clinical status might also be possible. Relation between AED changes and IED is a disputed topic: D'Antuono et al. describe that changes in AED did not show an effect on frequency of interictal-like-epileptic discharges in animal models.[37] In humans Gotman et al. failed to show a relation between AED levels and IED. However, in a more recent study with iEEG a significant decrease in IED occurred after AED withdrawal and changes in frequencies of

Table 2
Sensitivity of MEG and EEGsd in patients with neocortical focus and mesial temporal lobe focus (a). Comparison between sensitivity for neocortical and mesial temporal lobe focus of M/EEG and EEGsd in all patients, who had simultaneous M/EEG (b).

(a) 54 patients with hypothesis for epileptic focus						
Focus	MEG+	MEG−	EEGsd+	EEGsd−	MR+	MR−
Neocortical	25	12	23	14	24	13
Temporomesial	9	8	7	10	13	2
(b) 49 patients with hypothesis for epileptic focus, who had combined M/EEG						
Focus	M/EEG+	M/EEG−	EEGsd+	EEGsd−	MR+	MR−
Neocortical	24	10	21	13	22	12
Temporomesial	11	4	6	9	13	2

postictal interictal activity could be used to differentiate between neocortical and temporomesial foci. Although a correlation between seizure occurrence and IED could not be proven [38,39]. In the presented study alterations in AED and clinical status were accidental and should not be advantageous for any of the methods, but they might have biased the results.

As this project compares MEG (M/EEG) and EEGsd as two routine clinical diagnostic methods it is important to estimate the relevance of remaining differences adequately. In the study design, it was made sure, that MEG (M/EEG), which was compared to EEGsd, was never put in an obviously better position.

In this work, hypotheses for epileptic foci from assessment at the epilepsy center were used to choose primary recording position for MEG sensor. Subsequent control measurements at both hemispheres were performed, although they did not increase spike yield. Using a whole head MEG system could possibly increase sensitivity of MEG, as it increases sensor coverage of the brain and simplifies evaluation of multifocal epilepsies as no repositioning of the sensor is needed.

There is a mixed group of patients in this study with regard to age, etiology, type of epilepsy and stage of disease (drug resistant, untreated). However, the study population was less a group of patients within early stages of their epilepsy. The majority of patients included had drug resistant epilepsy, due to the selection bias of MEG. This might yield a higher occurrence of epileptic spikes in MEG (M/EEG) and EEGsd compared to patients who are evaluated in early diagnosis of epilepsy. However, this is not thought to be advantageous for any of the used diagnostic methods.

Nevertheless, results of our study underline the benefit of MEG in evaluation in this diverse group of patients. In our opinion, this study supports future prospective studies on the substitutability of EEGsd by MEG in epilepsy centers, where it is already available.

It could be argued, that there is no benefit by introducing MEG and simultaneous M/EEG in the early assessment of epilepsy patients, as this examination is expensive and technically complex. But in contrast to EEGsd this examination could be accomplished with outpatients. Beyond that, by significantly increasing the yield of electrophysiological assessment in complicated cases typically seen at an epilepsy center, best treatment and further diagnosis options could be chosen early and treatment costs could be diminished.

5. Conclusion

MEG and simultaneous M/EEG are valuable diagnostic tools to record epileptic activity. In our study, MEG has shown equal effectiveness compared to EEGsd in recording epileptic spikes with a tendency to register epileptic spikes in more patients. Using this highly sensitive tool to record epileptic activity would be of clinical importance in diagnosis and treatment monitoring of epilepsy, especially in patients with normal epilepsy MRI. As EEGsd is of debated significance, has an increased risk of seizure occurrence and stresses patients due to sleep deprivation, future studies should evaluate substitutability of EEGsd by MEG or M/EEG.

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